

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Single Technology Appraisal**

**Pembrolizumab with axitinib for untreated locally advanced or metastatic renal cell carcinoma**

**Final scope**

**Remit/appraisal objective**

To appraise the clinical and cost effectiveness of pembrolizumab with axitinib within its marketing authorisation for untreated locally advanced or metastatic renal cell carcinoma.

**Background**

Renal cell carcinoma (RCC) is a cancer that usually originates in the lining of the tubules of the kidney (the smallest tubes inside the nephrons) that help filter the blood and make urine. RCC is the most common type of kidney cancer (more than 80% of the cases)<sup>1</sup>. There are several subtypes of RCC, the main ones being clear cell (accounting for approximately 75% of cases), papillary and chromophobe<sup>1</sup>.

Early small RCC tumours are usually asymptomatic; the diagnosis of early RCC is often incidental after abdominal scans for other reasons. The most common presenting symptoms of advanced RCC are blood in the urine (haematuria), a palpable mass in the flank or abdomen and abdominal pain. Other non-specific symptoms include fever, night sweats, malaise and weight loss. RCC is classified into stages I to IV. Stage III denotes disease that is locally advanced and/or has spread to regional lymph nodes. Metastatic RCC, in which the tumour has spread beyond the regional lymph nodes to other parts of the body, is defined as stage IV. Surgery, including nephron-sparing surgery, radical nephrectomy and ablative therapies, is the main treatment for localised and metastatic RCC. However, around half of those who have surgery for localised RCC develop metastatic disease later on.

In 2015, 10,507 new kidney cancer cases were diagnosed in England<sup>2</sup>. Approximately 44% of people diagnosed with kidney cancer with a known stage in England and Northern Ireland have stage III or IV disease<sup>2</sup>. The 5-year relative survival rate ranges from approximately 83% at stage I to 6% at stage IV for patients diagnosed with RCC<sup>3</sup>.

The aim of systemic treatment with biological therapies for advanced disease is to stop the growth of new blood vessels within the tumour and to modulate the immune system to attack tumour. In untreated RCC, NICE has issued the following technology appraisal (TA) guidance:

- TA169 recommends sunitinib as a 'first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.'

- TA215 recommends pazopanib as a ‘first-line treatment option for people with advanced renal cell carcinoma who have not received prior cytokine therapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1’.
- TA512 recommends tivozanib for treating advanced renal cell carcinoma in ‘adults who have had no previous treatment’.
- TA542 recommends cabozantinib for ‘adults with untreated advanced renal cell carcinoma that is intermediate- or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria’.
- TA581 recommends nivolumab with ipilimumab ‘for use within the Cancer Drugs Fund as an option for adults with untreated advanced renal cell carcinoma that is intermediate- or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria’<sup>1</sup>.

**The technology**

Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. It is administered intravenously.

Axitinib (Inlyta, Pfizer) is an oral multi-targeted kinase receptor inhibitor with anti-tumour activity. Axitinib inhibits vascular endothelial growth factor receptor (VEGFR) -1, -2 and -3, platelet-derived growth factor receptor (PDGFR), and c-kit, which may result in inhibition of angiogenesis in tumours.

Pembrolizumab with axitinib does not currently have a marketing authorisation in the UK for untreated RCC. Pembrolizumab with axitinib is being studied in a clinical trial compared with sunitinib monotherapy in people with untreated locally advanced or metastatic RCC with clear cell component.

Axitinib has a marketing authorisation in the UK for treating advanced RCC after prior therapy, and this indication has already been appraised in NICE technology appraisal guidance 333.

<b>Intervention(s)</b>	Pembrolizumab with axitinib
<b>Population(s)</b>	Adults with untreated locally advanced or metastatic renal cell carcinoma

<sup>1</sup> Products recommended for use in the Cancer Drugs Fund after 1 April 2016 should not be considered as comparators, or appropriately included in a treatment sequence, in subsequent relevant appraisals. <https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisal-guidance/cancer-drugs-fund/CDF-comparator-position-statement.pdf>

<b>Comparators</b>	<ul style="list-style-type: none"> <li>• Tivozanib</li> <li>• Pazopanib</li> <li>• Sunitinib</li> <li>• Cabozantinib ('for disease that is intermediate- or poor-risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria')</li> </ul>
<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• overall survival</li> <li>• progression-free survival</li> <li>• response rates</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>
<b>Economic analysis</b>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out.</p> <p>The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any commercial arrangement for the intervention or comparator technologies will be taken into account.</p>
<b>Other considerations</b>	<p>Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.</p>
<b>Related NICE recommendations and NICE Pathways</b>	<p><b>Related Technology Appraisals:</b></p> <p><a href="#">Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma</a> (2019) NICE technology appraisal guidance 581. Review date</p>

	<p>August 2021.</p> <p><a href="#">Cabozantinib for untreated advanced renal cell carcinoma</a> (2018) NICE technology appraisal guidance 542. Review date October 2021.</p> <p><a href="#">Tivozanib for treating advanced renal cell carcinoma</a> (2018) NICE technology appraisal guidance 512. Review date March 2021.</p> <p><a href="#">Pazopanib for the first-line treatment of advanced renal cell carcinoma</a> (2011 updated 2013) NICE technology appraisal guidance 215. Static list.</p> <p><a href="#">Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma</a> (2009) NICE technology appraisal guidance 178. Static list.</p> <p><a href="#">Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma</a> (2009) NICE technology appraisal guidance 169. Static list.</p> <p><b>Appraisals in development (including suspended appraisals)</b></p> <p><a href="#">Atezolizumab plus bevacizumab for untreated locally advanced or metastatic renal cell carcinoma</a>. NICE technology appraisal guidance [ID1365]. Suspended.</p> <p><a href="#">Renal cell carcinoma – sunitinib</a>. NICE technology appraisal guidance [ID1076]. Suspended.</p> <p><b>Related NICE Pathways:</b></p> <p><a href="#">Renal cancer</a> (2015) NICE Pathway</p>
<p><b>Related National Policy</b></p>	<p>The NHS Long Term Plan, 2019. <a href="#">NHS Long Term Plan</a></p> <p>NHS England (2017) <a href="#">Manual for Prescribed Specialised Services 2017/18</a>. Section 105</p> <p>Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domain 1. <a href="https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017">https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017</a></p> <p>Independent Cancer Taskforce (2015) <a href="#">Achieving world-class cancer outcomes: a strategy for England 2015-2020</a></p> <p>Department of Health (2014) <a href="#">The national cancer strategy: 4th annual report</a></p> <p>NHS England (2013) <a href="#">B14. Cancer: Specialised kidney, bladder and prostate cancer services (Adult)</a>. NHS</p>

	<a href="#">Standard Contract.</a>
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**References**

1. Cancer Research UK [Types of kidney cancer](#). Accessed May 2019.
2. Cancer Research UK [Kidney cancer incidence statistics](#). Accessed May 2019.
3. Cancer Research UK [Kidney cancer survival by stage at diagnosis](#). Accessed May 2019.